NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON AGING

Summary Minutes

The 137th Meeting

NATIONAL ADVISORY COUNCIL ON AGING

May 21–22, 2019

National Institutes of Health
Building 60, Lecture Hall
Bethesda, MD 20892

CONTENTS

Department of Health and Human Services
Public Health Service
National Institutes of Health
National Institute on Aging

NATIONAL ADVISORY COUNCIL ON AGING
SUMMARY MINUTES
May 21–22, 2019

The 137th meeting of the National Advisory Council on Aging (NACA) convened on Tuesday, May 21, 2019, at 3 p.m. in Building 60, Lecture Hall, National Institutes of Health (NIH), Bethesda, Maryland. Dr. Richard Hodes, Director, National Institute on Aging (NIA), presided.

The meeting was closed to the public on Tuesday, May 21, from 3 p.m. to 5 p.m. for the review, discussion, and evaluation of grant applications, in accordance with the provisions set forth in Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of the Public Law 92–463.[1] The meeting was open to the public on Wednesday, May 22, from 8:00 a.m. to 1:10 p.m.

Council Participants:
Mr. James Appleby
Dr. David A. Bennett
Ms. Meryl Comer
Dr. Eileen M. Crimmins
Dr. Alison M. Goate
Dr. Margaret A. Goodell
Dr. J Taylor Harden
Dr. David M. Holtzman
Dr. Stephen B. Kritchevsky
Dr. Terrie E. Moffitt
Dr. Eric Michael Reiman
Dr. Clifford James Rosen
Dr. Amy Jo Wagers

Ex Officio Participants:

Absent Ex Officio Participants:
Dr. Alex Azar II, Department of Health and Human Services
Dr. Francis S. Collins, National Institutes of Health

The Council Roster, which gives titles, affiliations, and terms of appointment, is appended to these minutes as attachment A.

[1] For the record, it is noted that members absented themselves from the meeting when the Council discussed applications (a) from their respective institutions or (b) in which a conflict of interest may have occurred. This procedure only applied to applications that were discussed individually, not to "en bloc" actions.

In Addition to NIA Staff, Other Federal Employees Present:
Ms. Valerie Cosby, National Institute of Diabetes and Digestive and Kidney Diseases

Members of the Public Present:
Dr. Susan Alberts, Duke University
Dr. Randall J. Bateman, Washington University School of Medicine
Dr. Lydia A. Bazzano, Tulane University School of Public Health and Tropical Medicine
Dr. Shalender Bhasin, Harvard Medical School*
Mr. Phil Cronin, Cure Alzheimer's Fund
Ms. Trish D'Antonio, Gerontological Society of America/Friends of NIA
Dr. Monica Driscoll, Rutgers University*
Dr. Terry Fulmer, John A. Hartford Foundation*
Ms. Sheila Harley, BETAH Associates, Inc.
Dr. Bradley Hyman, Harvard Medical School
Dr. Catharine Krebs, Physician Committee for Responsible Medicine
Dr. Rose Maria Li, Rose Li and Associates, Inc.
Dr. Paolo Sassone-Corsi, University of California, Irvine
Dr. Keith Whitfield, Duke University*

*New Council members pending final approval

I. REVIEW OF APPLICATIONS

This portion of the meeting was closed to the public, in accordance with the determination that it concerned matters exempt from mandatory disclosure under Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix).[2]

A total of 1,853 applications requesting $3,578,316,023 for all years underwent initial review. The Council recommended 1,011 awards for a total of $2,237,005,814 for all years. The actual funding of the awards recommended is determined by the availability of funds, percentile ranks, priority scores, and program relevance.

II. CALL TO ORDER

NIA Director, Dr. Richard Hodes, welcomed members to the open session of the 137th NACA meeting and called the meeting to order at 8:00 a.m. on Wednesday, May 22, 2019.

A. Director's Status Report

Dr. Hodes reminded the Council that the 2019 NIH budget reflected an increase of $2 billion, for a total budget of $39 billion, marking a string of successive increases at NIH. This includes a $425 million increase targeted toward research on Alzheimer's disease (AD) and related

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dementias (ADRD). The NIA budget is now $3.1 billion, which includes a non-targeted increase of $84 million, a percent increase comparable to other Institutes and Centers (ICs). Dr. Hodes noted that all NIA programs benefited from this increase. The federal government is currently funded through September 30, 2019.

Overall, application success rates at NIH remain relatively stable, but success rates at NIA increased. In FY2018, the success rate at NIA was 28% to 29%, a range in which NIA could fund nearly all outstanding research applications it received. Recognizing that other NIH ICs have important contributions to make to AD/ADRD research, NIA also used some targeted AD/ADRD money to fund the Alzheimer's-related research of other ICs.

The budget for 2020 is unknown. The Senate has not yet produced any draft bills, but the House proposes an increase of $2 billion, including a 6.6% increase to a budget of $3.3 billion for NIA. However, the President's proposed budget includes a substantial decrease across all areas at NIH.

Dr. Hodes then discussed research updates. He noted the failures of some large, late-phase clinical trials for AD and commented that NIA, having learned from these trials, is now focusing on research targeting amyloid in the prodromal stages of AD. In addition, NIA is supporting clinical trials addressing a wide array of other targets, studies of non-pharmacological interventions, and studies focusing on AD care and caregiver interventions. Dr. Hodes also noted that NIA continues its spate of outstanding research accomplishments. Among the examples he presented was a recent New England Journal of Medicine article that highlighted the 12 most important papers in changing the practice of medicine in recent times. A Type 2 diabetes prevention trial, partially funded by NIA, was highlighted in that article. This study showed that metformin and lifestyle intervention among individuals with pre-diabetes could prevent the onset of diabetes. Dr. Hodes also reminded the Council about the iCare AD/ADRD Challenge, in which NIA is offering up to $400,000 in prizes to encourage the development of technological applications to improve dementia care coordination or navigation.

Among recent events is a congressional reception for the NIH Children's Inn, in which NIA and Representative Maxine Waters participated; a trip NIA Deputy Director Dr. Marie Bernard made with Senator Shelley Moore Capito to her home state of West Virginia; Dr. Hodes' testimony at a special Senate Committee on Aging hearing on AD; and the participation of several NIH IC Directors at hearings of the Senate Appropriations Committee. The third Geroscience Summit will be held November 4–5, 2019, and the second AD/ADRD Care and Services Summit will be held in March 2020. NIA has a notice seeking input to aid in planning this Summit, and the Council is invited to provide feedback. The notice is open through June 28. Dr. Hodes reminded the Council of the new NIH policy, partially based on a paper co-authored by Dr. Bernard, regarding the inclusion of older adults in clinical trials. He also noted new resources for the AD/ADRD research community, including the Alzheimer's and Dementia Outreach, Recruitment and Engagement Resources (ADORE) and the Harmonized Cognitive Assessment Protocol (HCAP).

Dr. Hodes closed his presentation by announcing new hires. Dr. Ned Sharpless, a former Council member, has joined the Food and Drug Administration as its Acting Commissioner. Dr. Noni Byrnes has been named Director of the NIH Center for Scientific Review, and Dr. Debara Tucci

has been named as Director of the National Institute on Deafness and Other Communication Disorders.

B. Future Meeting Dates

September 10–11, 2019 (Tuesday and Wednesday, Neuroscience Building, 6001 Executive Boulevard)
January 21–22, 2020 (Tuesday and Wednesday, Building 31)
May 26–27, 2020 (Tuesday and Wednesday, Building 31)
September 8–9, 2020 (Tuesday and Wednesday, Building 45)

C. Consideration of Last Meeting's Minutes

The minutes of the January 2019 meeting were considered. A motion to approve the minutes was made, seconded, and passed unanimously.

III. REPORT: TASK FORCE ON MINORITY AGING RESEARCH

Dr. David Bennett began by reminding the Council of its discussions at the January meeting regarding shortcomings in the triennial inclusion report. He reported that the Task Force co-chairs recommended that Council form a small committee that will work with Dr. Robin Barr to improve the report and present this improved report at each January Council meeting. Drs. Bennett, J Taylor Harden, Terrie Moffitt, and Clifford Rosen volunteered to serve on this committee.

A motion was made and seconded to form the small committee. Dr. Eileen Crimmins suggested that the committee could also make recommendations to Dr. Barr about ways in which NIH could improve reporting. Dr. Barr reminded the Council that the triennial report is mandated by Congressional legislation that requires a specific format. He also acknowledged that this format limits the value of the information it presents. Dr. Bernard noted that new legislation requires NIH to report demographic information by Research, Condition, and Disease Categorization. She acknowledged that this reporting might not be much more informative than the triennial report, but she invited Council members to learn more about that. The Council passed the motion unanimously.

Dr. Bennett also reported on several presentations the Task Force had heard the day before. One was a presentation concluding that Research Supplements to Promote Diversity in Health-Related Research are an important part of the pipeline moving diverse investigators toward independent research. The second, by Dr. David Wilson, reported on the NIH Tribal Health Research Office. A talk by Dr. Melissa Gerald, who provided an update on aging in sex and gender minority (SGM) populations, presented a glossary of terms, a list of NIA-supported databases with SGM measures, and a list of best practices for using those measures.

Dr. Bennett spent some time discussing a presentation by Dr. Dedra Buchwald, who provided an overview of ADRD among American Indians, Alaska Natives, native Hawaiians, and Pacific Islanders (AIAN or Native Americans). As with the general U.S. population, the AIAN population is aging; almost half a million Native Americans are over 65 years old, and that

number is expected to triple during the next 50 years. However, life expectancy among the AIAN population is approximately six years shorter than that among white individuals, and this population faces several demographic, socioeconomic, and clinical risk factors for AD. Dr. Buchwald and her colleagues have found that processing speed, memory, and general cognition are inversely associated with vascular brain injury, atrophy, a smaller brain, and a smaller hippocampus. They had also found that, among the AIAN population, the *ApoE2* allele appears less commonly than among the general U.S. population and the *ApoE4* allele appeared with the same frequency as it does among the general U.S. population. Dr. Buchwald now has a grant from the National Institute on Minority Health and Health Disparities to examine biomarkers of cognitive impairment and AD among American Indians. She and her colleagues also have a Resource Center for Minority Aging Research (RCMAR) grant with mentored pilot projects in Native American populations. Dr. Buchwald's presentation also described successes of the Native Investigator Development Program, a two-year training program that has been funded by NIA since 1988. Dr. Bennett commended Dr. Buchwald's group particularly for its efforts to engage Native Americans in research.

Dr. Bennett closed the presentation with updates from Dr. Carl Hill, which included an announcement that the Butler-Williams Scholars Program will be held July 29–August 2, 2019.

IV. REPORT: WORKING GROUP ON PROGRAM

A. RFA/RFP Concept Clearances

Dr. Eileen Crimmins reported that the Working Group reviewed eight concepts and recommended all of them for approval. A motion was made and seconded to approve these concepts en bloc. The motion passed unanimously.

Paul B. Beeson Emerging Leaders Career Development Award in Aging

Since 1984, when it was first funded by the John A. Hartford Foundation, the Atlantic Philanthropies, and the Moore Foundation, the Beeson program has been essential in recruiting and developing lead scientists in clinical and medical research. This concept proposes to renew the Beeson program.

Lipid Signaling in Health Span and Longevity Regulation

The proposed concept addresses gaps in understanding about the effects of lipid biology on health and quality of life in aging. It will support research on how lipid biology changes with age, where lipids are generated, how different tissues contribute to systemic differences in lipids, and how dietary lipids can contribute to extended lifespan and health span.

Resource Development to Support Basic Biology of Aging and Health Disparities Research

This concept proposes to support the development of a network within the Division of Aging Biology (DAB) for translational studies to address health disparities. DAB has proposed three strategic goals for this network: developing a better understanding of biological factors that diminish health and life expectancy; increasing health; and promoting translational research, primarily from mouse studies.

Biological Mechanisms of Metformin Effects on Aging and Longevity

Studies in several organisms have demonstrated the beneficial effects of metformin on longevity. However, the mechanisms underlying these effects are unknown. The proposed concept will support research to identify the major sites of action; the targets of metformin; and its effects on cell and tissue function, transport, metabolomics, and the microbiome.

Research on Biopsychosocial Factors of Social Connection and Isolation on Health, Wellbeing, Illness, and Recovery

The proposed concept will support research exploring the association between social isolation and loneliness and poor health and wellbeing. Many older adults live alone, making them vulnerable to poorer health. Part of the NIH Basic Behavioral and Social Science Opportunity Network, the concept will support broad approaches in this research. Other ICs might co-fund meritorious applications.

Creating a Network to Optimize Emergency Care of Persons with AD/ADRD

The proposed concept will fund a synergistic, transdisciplinary community of clinicians and investigators to establish research infrastructure to identify research gaps and design efficient and effective strategies to triage and manage persons with dementia. The Working Group noted that this concept aligns with NIA's expertise and strategic goals.

Implementation Research on Hypertension Control to Prevent Dementia and Cognitive Decline

This concept seeks to support the development of pragmatic trials on the effectiveness of disseminating hypertension control among older adults with multiple morbidities. These studies will include broad and diverse populations in real-world settings. The Working Group noted recent findings that more intensive blood pressure control might help in preventing cognitive decline in older adults. Group members also suggested that the concept introduce more innovative ways of assessing cognitive function that are more sensitive to change than previous methodologies.

Reissuance of Program Announcements with Special Review (PAR) on Research Infrastructure Development for Interdisciplinary Aging Studies

In 2016, NIA issued two program announcements to support interdisciplinary research. One focused on the initial development of infrastructure, and the other supported further development and use of that infrastructure. Nine awards receive funding through these announcements, which will expire in September 2019.

B. Review of the Division of Behavioral and Social Research (DBSR)

Dr. Crimmins provided an update on an ongoing review of the past five years at DBSR. She and Dr. Moffitt co-chair the review committee, and members include five Council members and one former Council member. The review committee is looking at cross-cutting themes, including AD/ADRD, basic science, interventions, health disparities, centers, and training. The review

committee expects to present draft recommendations at the September Council meeting and its final report at the January 2020 meeting.

C. Clinical Trials Advisory Panel (CTAP)

Dr. Robin Barr reported that CTAP looked at an application for a clinical trial investigating caloric restriction beyond the CALORIES trial. The application was brought forward for informational purposes, and no vote was taken. If the trial moves forward, a concept will be brought to Council for review.

V. MEETING NEW CHALLENGES: NIA COMMUNICATIONS AND OUTREACH

One aspect of the NIA mission is to disseminate information on health and research advances. As NIA evolves, it faces several opportunities and challenges, including outreach to new and established researchers about funding opportunities; translating new findings into health information; reaching diverse audiences for clinical trial recruitment; accountability and transparency to Congress and taxpayers; and collaboration and communication with new and existing groups. NIA must therefore communicate with a wide variety of audiences.

Ms. Cindy McConnell described the work of the NIA Office of Communications and Public Liaison (OCPL), which she directs, as communicating with researchers, older adults and caregivers, the media, and the general public. OCPL reaches the research community through such tools as a blog, Inside NIA; a webinar for grantees and potential grantees; and ResearchGate, a Facebook for researchers. OCPL also works with grantee institutions to coordinate information dissemination and supports clinical trial recruitment through a clearinghouse, clinical trials databases, electronic alerts, and ADORE. The Office works proactively to engage with journalists and the public, provide scientific and evidence-based information to older adults and caregivers through its website, and provide consumer health information through the NIA Information Center. All OCPL content is mobile friendly and accessible to individuals with disabilities. Ms. McConnell added that OCPL has a strong social media presence and that its website will soon be searchable by voice.

Ms. McConnell encouraged Council members to help OCPL amplify its messages. All content on the Office's public website is open for members to present at their own institutions, and Council members are invited to contact OCPL about journal articles published by their institutions so that the Office can help promote them.

Dr. Melinda Kelley described the work of the Office of Legislation, Policy, and International Activities (OLPIA), which she directs, as communicating with Congress, other federal agencies, professional societies, non-governmental organizations, and advocacy organizations. OLPIA manages special policy projects and is responsible for speechwriting and for preparing NIA leadership for external engagements. The Office also assists with the leadership's participation in congressional hearings, member briefings, and congressional visits to NIH, and it provides technical feedback on draft bills. OLPIA fosters communication and collaboration with stakeholder groups through domestic group meetings, facilitates meetings between NIA leadership and international groups, and conducts tailored follow-up after annual meetings. In addition, OLPIA coordinates the internal curation of scientific advances across NIA Divisions

and offices within the office of the NIA Director, works with HHS staff to provide AD updates to the National Plan, and serves as the lead in the Eureka Prize on using technology to improve care coordination for individuals with AD/ADRD.

Mr. James Appleby commended OCPL and OLPIA on its works, particularly its weekly communications with advocacy organizations.

Dr. Harden noted the importance of oral traditions and storytelling among Native American and other communities, and she suggested that NIA hold radio addresses, similar to one done weekly by Dr. Griffin Rodgers, Director of the National Institute of Diabetes and Digestive and Kidney Diseases, to provide updates about scientific advances. Drs. Hodes and Bernard were willing to consider such an approach. Ms. McConnell added that OCPL is also considering podcasts. Ms. Meryl Comer added that her organization is bringing patients and their families closer to the data through their own stories.

In response to other questions, Ms. McConnell noted that OCPL uses Twitter to disseminate information about AD research funding opportunities. Dr. Moffitt suggested that OCPL and OLPIA explore use of Altmetric, which can search the internet every 20 minutes for anything with a digital object identifier to track the reach of NIA-funded research.

VI. PROGRAM HIGHLIGHTS

A. DBSR: Wild Animal Models of Health and Aging: Innovations and Insights

Dr. Susan Alberts presented findings from the Amboseli Baboon Research Project, which has collected data on a wild baboon population in southern Kenya since 1971. Prospective, longitudinal, full life course research studies are at the heart of behavioral and science research, because they increase understanding of how earlier stages of life contribute to healthy aging. However, human studies are challenging. Datasets, especially those that include information from the entire life course, are scarce. Most are incomplete, and those that are complete rely on indirect measures or self-report. In addition, these studies are confounded by health habits and health care.

Studies in non-human primate (NHP) models, which have proven valuable in cellular and molecular biology studies, can overcome these challenges as social and behavioral models. Studies of wild primate populations have prospectively collected full life course data, including direct, real-time observations of social behaviors and environments. These primates have an accelerated life course compared with humans, such that studies can collect data more quickly on multiple generations. In addition, they exhibit complex social interactions, but these interactions are simple compared with human behaviors. Thus, NHP populations can provide simplified models of human societies.

The Ambolesi baboon population currently has 300 individuals and has had 1,800 total since the project began. The Amboseli Project has data on social interactions, environmental conditions, birth, maturation, and death. The project also has fecal samples from which investigators can measure steroid hormone concentrations and parasite loads and extract PCR-ready DNA. By building Cox proportional hazards models, Dr. Alberts and her colleagues have found that adult social interactions with both sexes predict survival among adult female baboons and that social

status has only an indirect effect. They also found that environmental conditions predict adult female survival. The addition of even one adverse condition, such as high social density, short intervals between siblings, maternal loss before four years of age, or low maternal social status, almost doubles mortality risk. Among individuals experiencing three or more adverse conditions, the median age at death is nine years, compared with 24 years among individuals with no adversity. Dr. Alberts also presented unpublished findings on the effects of females' early-life adversity on the survival of their offspring and associations between stress hormone levels and early mortality.

Dr. Alberts and her colleagues are looking more closely at the effects of social adversity. In particular, they are exploring whether social relationships and advantage in adulthood can mitigate the effects of early adversity, as well as the causal links between early adversity and outcomes in adulthood.

In response to questions, Dr. Alberts commented that the baboons are habituated to and thus unaffected by researchers and observers. Discussion focused on resilience, implications for replication in human studies, and technical aspects and challenges of Dr. Alberts's work.

B. Division of Neuroscience (DN): Dominantly Inherited Alzheimer Network (DIAN) Trials Unit (TU) — Next Generation tau Trials

Dr. Randall Bateman discussed the DIAN-TU as a public-private partnership established to change the course of AD. Recent years have seen an increased understanding of the molecular changes underlying AD. Accumulating evidence shows that AD is a process that begins decades before the onset of symptoms. It is characterized by the growth of amyloid plaques at least 10 years before symptoms appear. However, tau tangles appear at the time of symptom onset. Dominantly inherited AD, a rare form of AD, has been traced to inherited gene mutations in any one of three genes involved in amyloid beta (Aβ) production. These mutations are associated with a predictable age at onset, which is earlier than that seen with the common form of AD.

DIAN comprises sites in North America, Europe, Australia, and South America. Since its inception in 2008, DIAN has tracked amyloid plaques, tau tangles, and soluble tau species. A key advance has been the development of positron emission tomography (PET) tracers of AD-associated biomarkers such as tau. Using PET imaging, DIAN has found differences between sporadic AD and dominantly inherited AD in the deposition of tau tangles. The Network has also shown that these tangles are highly specific: they are not seen in family members without dominantly inherited mutations or in asymptomatic mutation carriers, but they do appear at the onset of symptoms in mutation carriers. In addition, by measuring phosphorylated tau species in cerebrospinal fluid (CSF), DIAN has found that different tau isoforms change at different stages of AD. In some cases, these changes are strongly concordant with the appearance of amyloid plaques, whereas other soluble tau species saw no such relationship.

Its first trial, which is exploring two monoclonal antibodies targeting different forms of Aβ, is reaching completion, and results are expected to be released in early 2020. DIAN-TU is also exploring these monoclonal antibodies in a secondary prevention trial. DIAN-TU has established a cognitive run-in period to collect biological information and biomarker signals from a cohort of participants before they enroll in a drug arm, and it will soon launch trial arms assessing tau-

based drugs, alone and in combination therapy, with the ultimate goal of identifying therapies for further studies in phase III registration trials. Dr. Bateman invited Council members to nominate tau drugs or combination therapies for study in these arms.

Council discussion focused on "the escapee," an individual with dominantly inherited AD mutations who is still asymptomatic long after the expected age of symptom onset. DIAN-TU is assessing why and how this individual has escaped the symptomatic implications of the mutation. Discussion also focused on the importance of CSF collection, potential differences between what is measured by PET scan and what is measured in the CSF, how to control for DIAN-TU participants who are moved to a new drug arm, and studies on the role of the innate immune system in AD pathophysiology.

C. Division of Geriatrics and Clinical Gerontology: A Lifespan Approach to Aging: Findings from the Bogalusa Heart Study

Dr. Lydia Bazzano presented data from the ongoing Bogalusa Heart Study. Bogalusa, Louisiana is a rural, low socioeconomic, black-white community with an average life expectancy of 73 years. The Bogalusa Heart Study was established in 1973 to understand the impact of cardiovascular and metabolic changes on health throughout the lifespan. It began with a sampling of 3- to 17-year-old children and has led to several substudies and publications examining various outcomes. In 2012, the study received funding to include cognitive and physical performance measures, epigenetic data, and magnetic resonance imaging (MRI) and microbiome data. Because the study has taken a lifespan approach, it offers the opportunity to assess the impact of early-life events on health outcomes in midlife and older age. The longitudinal repeated measures in the study also allow for causal modeling.

Dr. Bazzano presented data on the lifespan origins of health disparities. Arterial stiffness is higher among black individuals than white individuals, and blood pressure is elevated at earlier ages among black individuals. Data from the Bogalusa Heart Study showed links between cardiovascular factors and birth outcomes such as small gestational age and low birth weight, and racial differences in these outcomes. However, these differences were not sufficient to explain the racial disparities in arterial stiffness and blood pressure. Life course cardiovascular risk is fairly modifiable, but the presence of lower cardiovascular risk mobility at younger ages is more difficult to modify. If someone falls behind his or her peers at an early age, catching up by midlife is more difficult.

Dr. Bazzano described an assessment of the performance of five different diabetes risk scores, only one of which was developed in a population with substantial minority representation. This assessment found that all five risk scores showed discrimination and specificity in predicting lower risk but lacked sensitivity. It also found that current risk scores might identify young adults with lower-than-normal risk for diabetes, regardless of race. Dr. Bazzano also highlighted findings from the last funding period. Data from the Bogalusa Heart Study suggest an association between nulliparity and worse physical function, pregnancy complications and worse physical function, and the gut microbiome and lifetime risk for cardiovascular disease. Another project has identified 16 novel metabolites that are associated with arterial stiffness, independently of traditional cardiovascular risk factors. A pilot MRI study has shown that adolescents with high normal fasting glucose levels showed less fMRI activation and more white matter

hyperintensities in performing the Stroop test compared to those with normal glucose levels. Dr. Bazzano concluded her presentation by reviewing current and future directions for the study.

In response to questions, Dr. Bazzano noted that the Bogalusa Heart Study has the data to address questions about the association between hormonal changes at pubertal transitions and susceptibility to age-related phenotypes. She also noted that quantifying attrition has been difficult because of changes in the town population and because the Bogalusa Heart Study has shifted from a cross-sectional panel study to a continuous longitudinal study. However, the study has managed to follow more than 3,500 study participants, including those who are incarcerated.

D. Division of Aging Biology: Aging, Nutrition, and the Circadian Clock

Dr. Paolo Sassone-Corsi described his work investigating metabolomic changes along the circadian cycle. Circadian rhythms help organisms adapt to environmental changes such as travel, light, and seasons. They are based on highly conserved molecular machinery that are controlled primarily by regulatory transcriptional and translational loops and have been linked with chromosomal epigenetic control. Within the clock transcriptional regulatory loop, Bma1 and clock proteins serve as activators, whereas Per1, Per2, and Per3 serve as repressors. During the day, the repressors reside outside the nucleus, allowing transcription to proceed. By nighttime, the repressors have moved to the nucleus, where they interfere with transcription. Disruption of these clocks leads to conditions such as insomnia, depression and anxiety, metabolic disorders, inflammation, accelerated aging, obesity and diabetes, and even cancer.

Circadian clocks are always running. However, external cues are important to fix these oscillations with respect to environment. In mammals, the suprachiasmatic nucleus within the hypothalamus is a central pacemaker. However, this is not the only pacemaker. Several clocks exist in the periphery, and the central clock within the suprachiasmatic nucleus communicates with these peripheral clocks through humoral pathways. The number of genes controlled by these clocks is higher than initially assumed.

Dr. Paolo Sassone-Corsi and his colleagues have created a biocomputing resource to determine whether and where metabolites oscillate. They have found that nutritional challenges such as a high-fat diet can disrupt one clock, but they also start other clocks. Thus, the time that an organism eats is as important as what and how much the organism eats. Likewise, the timing of exercise is as important as the timing of food intake. Dr. Sassone-Corsi's group has also found that nutritional changes not only disrupt and rewire circadian clocks, but that they also disrupt the communication and coordination that is normally present among several clock systems.

Dr. Sassone-Corsi's group has generated a mouse model in which BMAL has been knocked out, disrupting all circadian clocks. As expected, these mice exhibit accelerated aging, age-related pathologies, and early mortality. When they introduce a cassette to restart a tissue-specific clock in the liver, recruitment of BMAL to the chromatin is restored. However, only 10% to 15% of oscillating transcripts and 20% of metabolites are restored to levels seen within wild-type mice. Moreover, these oscillations are restored in a normal light-dark cycle, but not in a dark-dark cycle, indicating that in the absence of other clocks, light must communicate with the clock in the liver. Dr. Sassone-Corsi's group is generating mouse models in which a second clock has been restored to determine how these clocks communicate.

Council questions focused on xenograft experiments, the implications of circadian disruptions for the sundowning phenomenon seen with AD, the identification of chronotypes among the widely variable clocks among humans, and the implications of Dr. Sassone-Corsi's work for populations.

VII. PLANNING FOR AN INTRAMURAL PROGRAM ON AD/ADRD

Dr. Bradley Hyman discussed the planned Center for Alzheimer's and Related Dementia (CARD), a collaborative initiative that will assemble foundational resources and expertise; establish an NIH-based magnet for new scientific initiatives across NIH ICs, academic institutions, foundations, and the private sector; and explore new ways to prioritize collaborations and progress, rather than focus solely on individual researcher success. Recent years have seen an unprecedented infusion of resources into the study of dementias. However, leveraging those resources in industry, academia, and NIH to prevent or treat AD/ADRD is challenging. New approaches are needed to galvanize new cutting-edge ideas, encourage translational research, and create infrastructure to support accelerated research for cures. The NIH Intramural Research Program (IRP) can serve as a catalyst by supporting external research and by expanding innovative translational research.

CARD will provide a new infrastructure and resources, serve as a source for expertise, and serve as a platform for new forms of collaboration. An advisory board, which will include basic science and clinical perspectives, will evaluate the direction and implementation of research, advise ICs on research funding in ADRD, introduce novel ideas for research on mechanisms and cures, and continuously track the progress of CARD. Intramural scientists from NIA and the National Institute of Neurological Disorders and Stroke will take the lead, but additional leadership in translational and clinical research will be recruited. CARD will include existing NIH IRP staff on temporary, joint appointments; early-stage investigators who could receive extramural funding at the end of their appointments; and short- and long-term visitors from various academic and private sector scientists. In addition, CARD will leverage existing core services at NIH, including the Imaging Center and the Clinical Center.

Dr. Hyman reviewed the proposed organization for CARD and presented a timeline. The Advisory Board has met, and the first concept has been reviewed by the Scientific Advisory Board. Initial experiments and analyses are expected to begin in June 2019. A temporary facility for CARD is expected to be completed by Spring 2022, a laboratory in Building 10 is expected to be completed by August 2021, and CARD is expected be at 100% capacity by 2024.

Dr. Shalender Bhasin agreed with the plan to recruit talent and build a facility for CARD. However, he suggested that NIH consider the hurdles that interfere with the recruitment of top talent to the IRP. For example, he noted that administrative structures, inflexibility of these structures with respect to regulatory processes, and restrictions on travel can discourage individuals from coming to NIH. Dr. Hodes acknowledged these challenges. He noted that recruiting a senior investigator might be particularly difficult if that investigator wants to have a large, personally directed research program. Dr. Hodes noted that CARD aims to bring together scientists with a common goal and mission. Dr. Hodes and Dr. Luigi Ferrucci also noted some flexibility with NIH's constraints. Suggestions from Council members to aid in recruitment included a blog from IRP scientists about what they like about working in the program and an

emphasis on short-term appointments to get people engaged and excited about working with CARD. Dr. Hodes and the Council agreed on the need to ensure that the right people and leadership are involved.

In response to questions from Dr. Harden, Dr. Hyman noted that because NIA has a strong behavioral and social science research presence, it is assumed that this will be part of CARD. He emphasized the importance of these fields being included in CARD.

VIII. ADJOURNMENT

The open session of the 137th meeting of the National Advisory Council on Aging adjourned at 1:08 p.m. on May 22, 2019. The next meeting is scheduled for September 10–11, 2019.

IX. CERTIFICATION

I hereby certify that, to the best of my knowledge, the foregoing minutes and attachments are accurate and complete.[3]

Richard J. Hodes, M.D.
Chairman, National Advisory Council on Aging
Director, National Institute on Aging

Prepared by Robin Barr, D. Phil
With assistance by Rose Li and Associates, Inc.

[3] These minutes will be approved formally by Council at the next meeting on September 10–11, 2019, and corrections or notations will be stated in the minutes of that meeting.